Dissertation

"ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCNOMA"

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CERTIFICATE

This is to certify that, the dissertation entitled **"ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCNOMA"** is the bonafide work done by **DR AARTHI V.S.**, during her **M.S. (General Surgery)** course **2016-2019**, done under my supervision and is submitted in partial fulfilment of the requirement for the M.S.(BRANCH-I)- General Surgery of The Tamilnadu Dr.MGR Medical University, May 2019 examination.

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DECLARATION

I, certainly declare that this dissertation titled **"ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCNOMA"** represents a genuine work of mine. The contributions of any supervisors to the research are consistent with normal supervisory practice, and are acknowledged.

I also affirm that this bonafide work or part of this work was not submitted by me or any others for any award, degree or diploma to any other University board, either in India or abroad. This is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery Degree Branch I (General Surgery).

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(POST GRADUATE)

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ABSTRACT

BACKGROUND

Locally advanced breast cancer (LABC) occurs relatively infrequently and poses a significant clinical challenge. Even with combined-modality therapy and the use of novel drugs, long-term disease-free survival is approximately 50%-70%[88], indicating that the optimal therapeutic approach for these patients has not yet been reached. Neo-adjuvant systemic therapy integrated into a multimodality program is the established treatment in LABC. Pathological response to neoadjuvant chemotherapy directly correlates with disease free survival and hence this study was undertaken.

AIM

- To assess the pathological response of neoadjuvant chemotherapy in locally advanced breast carcinoma.

MATERIALS AND METHODS

STUDY CENTRE: Institute of General Surgery , Madras Medical College and Rajiv Gandhi Government General Hospital , Chennai

DURATION OF STUDY: May 2017- September 2018

STUDY DESIGN: Observational study

SAMPLE SIZE: 30

INCLUSION CRITERIA:

- Age > 18 years
- Locally advanced carcinoma
- Willing for follow up

EXCLUSION CRITERIA

- Prior Breast Surgery
- Prior radiotherapy to breast

- Metastatic disease

ETHICS CLEARANCE: Yes

METHODOLOGY

- Patients aged >18 years presenting with malignant breast lump were evaluated.

- Diagnosis confirmed by core needle biopsy and grade and hormonal status assessed and metastatic work up done.

- Thirty patients who fulfilled the inclusion criteria were chosen and were sent for neoadjuvant chemotherapy.(FAC OR FAC+PACLITAXEL REGIMEN)

- Patients were followed up and response of tumor assessed clinically and modified radical mastectomy was done.

- Specimen was analyzed for pathological response and observations made.

RESULTS

Majority of the population belonged to the age group of 50-60 (33%). Of the 30 patients having locally advanced carcinoma 73% belonged to stage stage IIIA and

27% belonged to stage IIIB.Almost half of the patients were ER positive, PR positive and HER2 negative and 23% of the patients were triple positive.Triple negative and HER 2 positive patients were of equal distribution (17%).Percentage of ER and PR positive tumors were 67% each.Percentage of HER2 positive tumors were 40%.Postoperative assessment of specimen was done and pathological response graded according to Chevalier classification.

- 53% were of grade 4
- 30% were of grade 3
- 13%were of grade 2
- 3% was of grade 1

Only 17% of patient population showed pathological response to NACT 83% were non responders which could possibly be explained due to higher ER positivity and lower response.

CONCLUSION

Identifying which tumors are most likely to respond to specific agents and regimens could significantly improve prognosis. Clinical management of LABC could be modified based on advances in our knowledge of cancer biology and genomic profiling to a highly effective individualized approach

Keywords: LABC, neoadjuvant chemotherapy,pathological response

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INTRODUCTION

Globally, carcinoma breast is one of the commonest malignancies in women and it is the second most common cause of cancer related death in females. In India , it is the second most common cancer, first being carcinoma cervix. According to National Cancer Registry Programme, breast cancer accounts for about > 30% of all cancers in Indian women where urban areas hold the highest incidence.[1,2]

Locally advanced breast carcinoma refers to a diverse and heterogeneous group of breast cancer and represents about 10 – 20% of all breast cancers in the developed world 5, while in India this group comprises about 60% of cases.

Globally, definition of Locally Advanced Breast Carcinoma is notuniform in various centres. Recent guidelines of U.S National Comprehensive Cancer Network classified locally advanced breast cancer as AJCC stage III. It includes:

- Tumour > 5 cms with regional lymph node involvement (N1-N3)
- Tumours of any size with chest wall or skin involvement or both, regardless of regional lymph node involvement.
- Presence of regional lymph node involvement irrespective of tumour size
- Fixed / matted axillary lymph nodes

- Infraclavicular / supraclavicular lymph nodes
- Internal mammary lymph nodes

(Note: In the 7th edition of AJCC – 2010, ipsilateral supraclavicular lymph node involvement was reclassified as regional lymph node involvement)

Based on probability of getting histologically negative margins after initial surgery, locally advanced breast carcinomas are classified as operable and inoperable. According to NCCN guidelines -2017:

1) Operable LABC : T2N1M0, T3 N0-1 M0

2) Inoperable LABC : Stage IIIA except T3N1M0 , Stage IIIB, Stage IIIC

(Note : NCCN Panel accepts the definition of negative margin as "No ink on the tumour," - 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins)

In the past, inflammatory breast carcinoma was considered as a subtype of locally advanced breast carcinoma.[6] On comparison with noninflammatory forms of locally advanced breast carcinoma, inflammatory breast cancer carries a poor prognosis. So separate guidelines were formed for its management.

Until the middle of last century, primary treatment of LABC was radical mastectomy. This did not change until Stout et al ,[4,5]identified the markers of poor outcome such as skin ulceration, oedema, tumour fixation etc. The Oxford review stated that the use of systemic therapy to treat micro metastasis, significantly reduces the risk of recurrence and death.

Neoadjuvant therapy, a newer modality of treatment evolved during the last three decades, is being practised all over the world for down staging technically inoperable locally advanced breast cancer prior to surgery. The literal meaning of the term neoadjuvant refers to a “new” (Greek) treatment added to “ assist” (Latin) a primary treatment. The biological rationale for neoadjuvant therapy for breast carcinoma is based on the observation of accelerated metastatic growth following tumour resection in animal models.

Neoadjuvant chemotherapy is established as standard treatment for LABC with varying pathological response rate.[7] There is significant association between the extent of pathological response and longterm outcome in terms of disease free survival- DFS and overall survival-OS[8]

This study was conducted to assess the pathological response of neoadjuvant in locally advanced breast carcinoma.

AIMS

- To assess the response to neoadjuvant chemotherapy in cases of locally advanced breast carcinoma

REVIEW OF LITERATURE

According to Globocan 2012, India along with United States and China collectively accounts for almost one third of the global breast cancer burden. India is facing challenging situation due to 11.54% increases in incidence and 13.82% increase in mortality due to breast cancer during 2008–2012.[9,10] The main reasons for this observed hike in mortality is due to lack of inadequate breast cancer screening, diagnosis of disease at advanced stage and unavailability of appropriate medical facilities. Breast cancer attains top rank even in individual registries (Mumbai, Bangalore, Chennai, New Delhi and Dibrugarh) in females during the period of 2012–2014.

Factors as marital status, location (urban/rural), BMI, breast feeding, waist to hip ratio, low parity, obesity, alcohol consumption, tobacco chewing, smoking, lack of exercise, diet, environmental factors were major risk factors in India leading to increasing incidence cancer; however, the reason for high incidence of breast cancer in younger women are not well known. Delayed disease presentation due to illiteracy, lack of awareness, financial constrains in some regions of India leads to late diagnosis, which in turn increases mortality rate. Lack of organized breast cancer screening program, paucity of diagnostic aids, and general indifference toward the health of females in the predominantly patriarchal Indian society are also the drawbacks leading

to increased breast cancer incidence. Hence majority of patients here are still treated at locally advanced and metastatic stages.[11]

LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer is a subset of breast cancer characterized by the most advanced breast tumours in the absence of distant metastasis. The need to identify labc as a separate group of breast cancers arose in view of the high associated rate of locoregional and systemic failure (in the absence of distant metastasis at presentation) despite the best efforts of surgeons to remove locoregional spread of the tumour in its entirety.[12]

The earliest therapy for locally advanced breast carcinoma was radical mastectomy[13]. However patients with supraclavicular lymphadenopathy, oedema of arm, satellite skin nodules, and extensive breast oedema were all found to develop recurrences and these signs were considered markers of inoperable disease. Patients who were treated with primary radiotherapy also had a high risk for disease recurrence and death, as well as the complications of chest wall fibrosis, brachial plexopathy, lypmhedema, skin ulceration, and skin necrosis[14].The first reports of the use of systemic chemotherapy for locally advanced disease was published in the 1970s.[15]Since then, the use of systemic chemotherapy has become standard and has substantially improved the prognosis of locally advanced breast carcinoma.

Patients with locally advanced breast cancer are at high risk of relapse and death as a result of metastatic disease. The long-term outcome of these patients is rarely reported. The National Cancer Database statistics show that patients with stage III disease who underwent modified radical mastectomy and both radiation and systemic treatment have a 3-year relative survival rate of 68%, a 5-year relative survival rate of 50%, and a 10-year relative survival rate of 36%.[16] The National Cancer Institute investigated the outcome of 61 patients with noninflammatory stage III breast cancer who received neoadjuvant chemotherapy and hormonal adjuvant treatment. Patients who had a complete response received definitive radiotherapy to the breast and axilla and patients with residual disease underwent mastectomy, lymph node dissection, and radiotherapy. The 15-year overall survival was 50% for stage IIIA and 23% for stage IIIB breast cancer.[17]

In a series of 831 patients with locally advanced breast cancer treated at the M.D. Anderson Cancer Center between 1974 and 1991 in clinical trials with neoadjuvant anthracyclinebased chemotherapy regimens followed by surgery or radiation therapy, the median follow-up duration was 69.9 months. Patients with locally advanced breast cancer included 490 (59%) with inoperable disease at diagnosis. The 5-year recurrence-free and overall survival rates were 56% and 63%, respectively[18]. Locally advanced breast cancer comprises a heterogeneous group of tumors, with marked variations in outcome that depend on the TNM stage and the molecular characteristics of the tumor. It is anticipated that the introduction of highly effective systemic agents

such as taxanes, trastuzumab, lapatinib, and the aromatase inhibitors will lead to an improvement in the survival of these patients.

DIAGNOSIS

Like all breast cancers, locally advanced breast cancer can be detected during physical examination or with mammography. Because these tumors are large and most are easily palpable, diagnosis can be established by a core needle biopsy. Estrogen receptor (ER) and progesterone receptor (PR) status, nuclear grade, and presence of HER2/neu, p53, and Ki67 can all be determined on the basis of histologic examination of tissue obtained by core biopsy. It is important that radiopaque clips be placed at the time of biopsy of suspicious areas to provide localization of disease for future surgical planning, especially if the patient may be a candidate for neoadjuvant chemotherapy.

Once invasive breast cancer is diagnosed, the patient should undergo a full staging evaluation to determine the extent of disease. Diagnostic bilateral mammograms are essential to determine whether any other clinically occult lesions are present in the same or contralateral breast. Ultrasonography is not always necessary but can be useful to measure tumor size, especially in women with dense breasts, and to determine whether axillary, infraclavicular, or supraclavicular nodes are involved. Breast magnetic resonance imaging (MRI) in addition to mammography or mammography and ultrasound has been shown to more accurately delineate the extent

of local disease and identify patients for whom breast-conserving surgery would be contraindicated[19].The routine use of MRI for the staging of patients with breast cancer has been limited by the lack of proven benefit that it reduces local recurrences and mortality[20].

After the extent of local-regional disease has been established, patients should undergo evaluation for systemic disease. All patients should undergo a thorough physical examination. Recommended staging studies are laboratory evaluation, including complete blood count, platelets, liver function tests, alkaline phosphatase, and chest radiography. Patients in whom any abnormalities are detected on laboratory evaluation or suggested by history and physical examination should undergo abdominal imaging with either ultrasonography or computed tomography (CT) and nuclear medicine bone scan. Other tests, such as CT of the chest or brain and MRI scans, should be performed if indicated on the basis of physical examination or by the presence of symptoms.

Small studies of less than 50 patients have described the use of F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in the staging of patients with locally advanced breast cancer. The detection rates of confirmed distant metastatic disease ranged from 8% to 14%, and the rates of false-positive results in the studies ranged from 0% to 21%[21]. FDG-PET is superior to CT in the detection of internal mammary and mediastinal lymph node metastasis; however, the impact of the increased sensitivity on clinical management and patient outcome is not known[22].

Currently, there is insufficient evidence to support the routine use of FDG-PET for the initial staging evaluation of breast cancer[23].

PROGNOSIS

Prognostic factors for locally advanced breast cancer are, in general, similar to those for breast cancer at other stages. Tumor size and site of regional lymph node metastasis (i.e., axillary, infraclavicular, supraclavicular, or internal mammary), which make up the basis of the current staging system, have the greatest impact on disease recurrence and survival [24]. There is a strong association between survival rates and number of involved nodes, with one study reporting 5-year survival of 73% for patients with metastases in one to three lymph nodes, compared with 46% for patients with metastases in four or more nodes [25]. The vast majority of these patients did not receive chemotherapy. Increasing size of the primary tumor also has prognostic significance for patients with breast cancer, even in women with tumors larger than 5 cm in diameter[26]. Data from the San Antonio database indicate that patients with tumors measuring 5 to 6 cm in diameter have a 5-year disease-free survival rate of 72%, compared with 57% for patients with tumors larger than 6 cm. Tumor expression of ER and/or PR is generally considered a weak favorable prognostic factor and is highly predictive for response to hormonal treatment. HER2/ neu-positive versus HER2/neu-negative status has been associated with a poorer prognosis in patients with lymph node–positive disease in the majority of studies[27]. HER2/ neu

is also a strong predictor of response to trastuzumab and anthracycline-based chemotherapy[28].

In the recently updated American Society of Clinical Oncology (ASCO) guidelines for the use of tumor markers in breast cancer, the routine evaluation of novel tumor markers such as urokinase plasminogen activator (UPA) and plasminogen activator inhibitor (PAI)-1, p53, cathepsin, cyclin E, and the Oncotype DX assay were not recommended for patients with lymph node–positive breast cancer. More recently, advances in microarray technology have allowed for further classification of breast tumors based on the expression of genes that correlate with survival and response to chemotherapy. In a cohort of 51 patients with locally advanced breast cancer (T3–T4 and/or N2 tumors) treated uniformly with doxorubicin chemotherapy, there was a significant decrease in the prognosis of patients with tumors classified as basal type compared with those classified as luminal type[29].Molecular classification of both lymph node–positive and lymph node–negative breast cancers using a 70-gene expression signature was more accurate than standard criteria such as the National Institutes of Health (NIH) Consensus and the St. Gallen criteria in predicting patients at high risk for recurrence[30].Prospective randomized trials are currently underway to evaluate the clinical utility of molecular profiling of breast tumors for prognosis and prediction of response to hormonal therapy and chemotherapy.

EVOLUTION OF LOCAL THERAPY

Historically, patients with locally advanced disease have been treated with radical mastectomy if technically possible. In 1943 Haagensen and Stout [13], two surgeons at Memorial Hospital in New York, published the results of surgical treatment in 1040 patients with breast cancer. They identified eight factors that were associated with uniform recurrence: distant metastases, inflammatory carcinoma, supraclavicular lymph node involvement, edema of the arm, satellite breast skin nodules, intercostals or parasternal nodules, extensive edema of skin over the breast, and carcinoma that developed during pregnancy or lactation. Haagensen and Stout concluded that any of these signs of advanced disease made a tumor "categorically inoperable." These authors also defined five "grave signs": skin ulceration, edema of limited extent, fixation of tumor to the chest wall, axillary lymph nodes greater than 2.5 cm in diameter, and fixed axillary lymph nodes. Any patient who had two or more of these signs was also considered to have inoperable disease because, in their series, only one of such patients was without disease recurrence at 5 years.

Thus, the authors recommended that surgery not be performed in patients with locally advanced disease who had the worst prognoses[13].The overall survival rates for patients with locally advanced breast cancer treated with surgical therapy alone remained poor. Failure of mastectomy alone to produce good survival rates prompted the use of primary radiation therapy for locally advanced tumors, especially those that were

considered inoperable. The results of multiple series indicated however that radiation alone was inadequate for patients with locally advanced disease[31].

For patients who are treated with primary radiation therapy, a high dose of radiation was deemed necessary to optimize local control [32].However, the high doses of radiation necessary to achieve local control were associated with considerable complications, including chest wall fibrosis, brachial plexopathy, lymphedema, skin ulceration, and rib necrosis[33]. Combined modality therapy that includes surgery and radiation therapy in patients with locally advanced disease has resulted in local control rates of 70% to 86%[34]. Patients with locally advanced disease benefit from local therapy, but the inadequate cure rates associated with such an approach clearly necessitate that systemic therapy be used.

COMBINED MODALITY TREATMENT

A combined modality approach that incorporates radiotherapy, surgery, or both; systemic therapy that includes chemotherapy and targeted agents such as trastuzumab; and hormonal therapy when indicated is currently widely used for the management of patients with locally advanced disease. This multimodality approach requires careful planning and coordination between the surgeon, medical oncologist, radiation oncologist, and diagnostic specialist but offers the optimal chances of patient cure.

The additional benefit of chemotherapy to surgery and radiation was demonstrated in a randomized study of 120 patients with operable stage III breast cancer who were

randomized after modified radical mastectomy to receive radiation therapy alone; vincristine, doxorubicin (Adriamycin), and cyclophosphamide (VAC) chemotherapy alone; or radiotherapy and VAC chemotherapy. The disease-free survival was better with combined modality of radiation and chemotherapy than with surgery alone ($P < 0.001$), and the 3-year overall survival rates were 57% for patients who received radiation therapy alone, 72% for those who received chemotherapy alone, and 90% for those who received both chemotherapy and radiation therapy ($P < 0.01$)[35]. These early findings supporting a role for adjuvant chemotherapy were confirmed by data from the Early Breast Cancer 2005 Trialists' Collaborative Group in their meta-analysis of worldwide experience with adjuvant chemotherapy versus no adjuvant chemotherapy in randomized clinical trials of approximately 150,000 women. These data demonstrated that adjuvant polychemotherapy produced highly significant reductions in mortality at 15 years of follow-up in women with node-positive breast cancer, and survival was better with anthracycline-based regimens than with regimens based on cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy[36].

Neoadjuvant chemotherapy is now preferred for patients with locally advanced breast cancer because it can downstage tumors and thus increase the rate of breast-conserving surgery. In cases of more advanced disease, neoadjuvant chemotherapy can render inoperable tumors resectable. Equivalent overall survival has been shown for patients who receive neoadjuvant versus adjuvant therapy[37]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 study involved 1523 women with T1–T3, N0–N1, and M0 operable breast cancer who were randomized to receive

either four cycles of doxorubicin plus cyclophosphamide given in the neoadjuvant setting or four cycles of the same regimen given as adjuvant therapy. At 16 years of follow-up, comparison of the neoadjuvant and adjuvant arms revealed no differences in the 5-, 8-, and 16-year rates of disease-free survival. There was a trend in favor of neoadjuvant chemotherapy compared with adjuvant chemotherapy for disease-free and overall survival in women younger than 50 years of age[37].

Similar findings were reported by the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group randomized trial of neoadjuvant versus adjuvant chemotherapy in patients with operable breast cancer. In this trial, 698 patients with stage T1c–T4b, N0–N1, and M0 operable breast cancer received either four cycles of neoadjuvant chemotherapy with fluorouracil, epirubicin, and cyclophosphamide (FEC), followed by surgery or surgery followed by four cycles of FEC. At a median follow-up of 56 months, there were no significant differences between the two arms in overall survival, progression- free survival rates, or time to local-regional recurrence.

The optimal regimen, duration, and sequencing of neoadjuvant chemotherapy has not yet been determined. However, the National Comprehensive Cancer Network (NCCN) guidelines indicate a preference for neoadjuvant regimens that contain both an anthracycline and taxane for patients with locally advanced breast cancer given the superior outcome of these regimens in the adjuvant setting for patients with lymph node–positive disease[38]. Among patients with HER2/neu-positive tumors, neoadjuvant

trastuzumab-, taxane-, and anthracycline- based regimens yield significantly higher clinical complete response (cCR) and pathologic complete response (pCR) rates,[39] although follow-up is still needed for long-term assessment of disease-free and overall survival. Adjuvant hormonal therapy with tamoxifen for premenopausal women[39] or aromatase inhibitors for postmenopausal women [41] improves disease-free survival and is incorporated into the systemic management of patients with locally advanced breast cancer as indicated based on the ER and PR status of the tumor.

The NCCN guidelines recommend postmastectomy radiation for all patients with pathologic confirmation of four or more positive axillary lymph nodes, T3 tumors, or clinical stage III disease [42]. However, a consensus has not been reached regarding the efficacy of postmastectomy radiation in patients treated with neoadjuvant chemotherapy.

The ASCO guidelines state that there are "insufficient data" to support a role for postmastectomy radiation for patients treated with neoadjuvant chemotherapy[43]. In a retrospective review of 150 patients (48% with stage IIIA or IIIB disease) treated with neoadjuvant chemotherapy followed by mastectomy at the M.D. Anderson Cancer Center, the 5- and 10-year rates of local-regional recurrence were both 27%. In patients with clinical stage III disease at diagnosis, the 5-year local-regional recurrence rate was 20%. In patients with clinical stage III disease who attained a pCR, the 5-year local-regional recurrence rate remained elevated at 33%. Increased pathologic tumor size and number of residual involved lymph nodes were associated with higher 5-year rates of local-regional recurrence[44].

Data from the NSABP B-18 and NSABP B-27 studies that randomized stage II and III patients to receive neoadjuvant or adjuvant chemotherapy prohibited the use of postmastectomy radiation, and patients who underwent lumpectomy received breast radiation only. In both studies, post-treatment pathologic lymph node involvement was a strong predictor of disease-free and overall survival ($P < 0.0001$)[37].

There are no randomized studies evaluating the benefit of postmastectomy radiation in patients treated with neoadjuvant chemotherapy. Huang and colleagues compared the outcome of 542 patients (73% with stage III disease) enrolled on several neoadjuvant chemotherapy trials who received mastectomy and radiation with a cohort of 138 patients (46% with stage III disease) who received similar treatment but who did not receive radiation. Patients who received postmastectomy radiation had a lower 10-year rate of local-regional recurrence (8%) compared with those who did not receive radiation (22%). Radiation also significantly improved the overall and cause-specific survival in patients with stage IIIB and IIIC disease and patients with four or more residual involved lymph nodes[45].It is recommended that patients with baseline tumor characteristics that predict an increased risk of local-regional recurrence receive postmastectomy radiation after neoadjuvant therapy regardless of clinical response[46]. This clinical practice requires the early involvement of the radiation oncologist in the multidisciplinary treatment planning of patients with locally advanced breast cancer.

Neoadjuvant chemotherapy for the treatment of breast cancer was introduced in the 1970s for patients with locally advanced disease. The terms neoadjuvant, primary, preoperative, and induction are all used to describe systemic chemotherapy given as initial therapy. Giving chemotherapy before other treatments has many theoretical advantages. Neoadjuvant chemotherapy can result in downstaging of tumors, thus increasing the rate of breast-conserving surgery. In cases of more advanced disease, neoadjuvant chemotherapy can render inoperable tumors resectable. Other advantages of neoadjuvant therapy include the ability to obtain information on tumor response, which can be used to study the biologic effects of chemotherapy and determine long-term disease-free and overall survival[47].Although neoadjuvant chemotherapy is recommended in the NCCN guidelines for the management of women with locally advanced operable or inoperable breast cancer, it can be offered to all patients who would otherwise receive adjuvant chemotherapy[48].

The NCCN guidelines indicate a preference for neoadjuvant regimens that contain both anthracycline and taxane for patients with locally advanced breast cancer.[42] Dieras and colleagues compared neoadjuvant doxorubicin with cyclophosphamide (AC) and doxorubicin with paclitaxel (AP), and higher cCR and pCR rates were associated with AP (cCR 15%, pCR 16%) than AC chemotherapy (cCR 7%, pCR 10%). Breast-conserving surgery was more frequent in the AP arm (58%) than the AC arm (45%; P value not provided).[49] Similar findings of a higher cCR and pCR were seen in the Anglo-Celtic Cooperative Oncology Group study that compared the combination of doxorubicin with docetaxel (AD) and AC. However, breast-

conserving surgery rates were equivalent (20%).[50] Steger and associates investigated whether six cycles of epirubicin and docetaxel (EC) resulted in a higher rate of pCR than three cycles of the same regimen in 262 breast cancer patients with stage II and III disease. Six cycles of EC compared with three cycles of EC resulted in a higher pCR (18.6 vs. 7.7%, respectively, P ¼ 0.0045) and a trend toward a higher rate of breast-conserving surgery.[51]

Several randomized studies have also investigated the sequential administration of taxanes following an anthracycline-based regimen and have showed higher rates of pCR. In the NSABP B-27 study, which included 2344 patients with stages II and III breast cancer, all patients were assigned to receive four cycles of doxorubicin and cyclophosphamide (AC) before surgery. Group 1 received no further treatment, group 2 received sequential neoadjuvant docetaxel for four cycles, and group 3 received adjuvant docetaxel for four cycles. Following surgery and radiation for patients who underwent lumpectomy, all patients received tamoxifen regardless of age or ER or PR status. Eighty-six percent of patients who received neoadjuvant AC alone (groups 1 and 3) experienced a clinical response compared with 91% of patients who received neoadjuvant AC and sequential docetaxel chemotherapy (P < 0.001). The cCR rate increased from 40% to 60% with the addition of neoadjuvant docetaxel, and the pCR rate increased from 13% to 26%. The improvement in pCR with the addition of docetaxel did not translate into an improvement in disease-free or overall survival, although relapse-free survival favored the neoadjuvant docetaxel arm.[37]

Similar findings were seen in the German Preoperative Adriamycin Docetaxel study, which randomized 904 patients with stage II and III breast cancer to receive four cycles of doxorubicin (Adriamycin) and docetaxel (AD) chemotherapy or four cycles of AC chemotherapy followed by four cycles of docetaxel. The arm that contained sequential administration of docetaxel resulted in a higher pCR (14.3%) compared with the combination arm (7%; P < 0.001).[52] The sequential administration of taxanes also provides benefit for patients who fail to respond to an anthracycline- based neoadjuvant regimen. In a study of 167 patients with locally advanced breast cancer, responders to four cycles of neoadjuvant cyclophosphamide, vincristine, doxorubicin, and prednisolone (CVAP) chemotherapy were randomized to receive either four additional cycles of CVAP or four cycles of docetaxel; nonresponders were all treated with four cycles of docetaxel. Patients who received docetaxel showed significantly higher clinical and pathologic response rates and significantly better 3-year survival rates (97% vs. 84%, P ¼ 0.02).[53]Caution should be taken when comparing the rates of cCR and pCR between neoadjuvant studies because of the different criteria used to define these outcomes.[48] A pCR defined by the complete eradication of invasive disease in both the breast and the lymph nodes is a prognostic factor for improved disease-free survival, and patients who attain a pCR have been shown to have improved overall survival.[54]

NEOADJUVANT TRASTUZUMAB BASED THERAPY

Trastuzumab has been integrated into the neoadjuvant setting in combination with chemotherapy for the treatment of patients with locally advanced breast cancer. In the majority of studies, tumors were considered HER2/ neu-positive if the immunohistochemical (IHC) assay (DAKO) showed 3þ staining or there was gene amplification by fluorescent in situ hybridization (FISH). Because of concerns regarding the elevated rate of cardiac toxicity [55] associated with the combination of anthracyclines and trastuzumab, neoadjuvant studies have focused predominantly on combining trastuzumab with taxane-based regimens. Limentani and coworkers evaluated the neoadjuvant combination of six cycles of docetaxel and vinorelbine given every 2 weeks with weekly trastuzumab for 12 weeks in 31 patients with locally advanced breast cancer, and they observed a clinical response rate of 94% and a pCR of 39%.[56] Burstein and colleagues treated 40 patients with stage II and III breast cancer (eight with HER2/neu IHC 2þ) with neoadjuvant paclitaxel every 3 weeks for four cycles with 12 weeks of trastuzumab. There was a 75% rate of clinical response (84% in patients with HER2/neu IHC 3þ vs. 34% in patients with HER2/neu IHC 2þ) and a pCR of 18%.[57] Increased pCR rates were also observed in a multicentered study of 70 patients with stage II and III operable breast cancer who received docetaxel and carboplatin for six cycles with weekly trastuzumab. Clinical response and pCR were observed in 95% and 37% of patients, respectively.[38]

Wenzel and associates conducted a pilot study to determine the feasibility, toxicity, and efficacy of the neoadjuvant combination of epirubicin, docetaxel, and trastuzumab in patients with early-stage breast cancer. At a median follow-up of 2 years, there was no significant decline of left ventricular ejection fraction and no clinical heart failure.[58] The safety profile demonstrated in this pilot study was also shown in the neoadjuvant trial by Buzdar and coworkers of 42 patients with T1–3, N0–1 and M0 disease who were randomized to receive paclitaxel every 3 weeks for four cycles followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) for four cycles versus paclitaxel every 3 weeks for four cycles with trastuzumab for 12 weeks followed by FECfor four cycles with trastuzumab for 12 weeks. The study was closed prematurely because of an unequivocal advantage for the arm containing trastuzumab. There was a pCR of 26% in the chemotherapy and 60% in the trastuzumab arm.[37]At a median follow-up of 36 months, the disease-free survival was 85% and 100% for patients in the chemotherapy and trastuzumab arms, respectively, and no patient developed clinically apparent cardiac toxicity.[59]These small studies demonstrated promising increased efficacy of trastuzumab-based neoadjuvant chemotherapy regimens for patients with HER2/neupositive tumors; however, long-term follow-up to determine disease-free and overall survival in addition to toxicity is needed.

NEOADJUVANT HORMONAL THERAPY

The role of neoadjuvant hormonal therapy for patients with ER-positive and/or PR-positive, large operable, and locally advanced breast cancer has been assessed in several studies. Tamoxifen was first investigated as an alternative to surgery in elderly patients with large operable tumors with the goal of determining whether surgery could be avoided in a selected population of elderly patients.Local failure rates were higher in patients treated with tamoxifen alone, but none of the studies showed a benefit for surgery in decreasing the development of distant metastatic disease. These studies demonstrated that hormonal therapy is an effective alternative for elderly women with locally advanced disease who have a limited life expectancy.

Randomized trials have since been conducted comparing tamoxifen with the aromatase inhibitors in the neoadjuvant setting. Ellis and colleagues reported a randomized trial of tamoxifen versus letrozole in postmenopausal patients with hormone receptor–positive tumors who were not candidates for breast-conserving surgery. Overall, 60% of patients treated with letrozole responded, and 48% underwent successful breast-conserving surgery. In the tamoxifen arm, 41% of patients responded, and 36% underwent breast-conserving surgery.[60]

In the Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) trial, postmenopausal women with ER-positive operable and locally advanced potentially operable breast cancer were randomized to receive neoadjuvant

tamoxifen, anastrozole, or a combination of the two agents for 3 months. There was no significant difference in the approximately 36% clinical response rate among the three treatment arms. Patients who received anastrozole alone had a higher rate of breast-conserving surgery (44%) compared with patients who received tamoxifen alone (31%).[61] The Preoperative Arimidex Compared with Tamoxifen (PROACT) trial enrolled 451 postmenopausal women with ER-positive and/or PR-positive large operable and inoperable breast cancer. Patients could receive concomitant chemotherapy, and surgery was planned after 3 months. The overall objective response rates were 39.5% with anastrozole versus 35.4% with tamoxifen. In patients who received neoadjuvant hormonal therapy alone, 43% and 31% treated with anastrozole and tamoxifen, respectively, were able to undergo breast-conserving surgery.[62] Although randomized studies have established the potential superiority of neoadjuvant aromatase inhibitor therapy for clinical response, the pCR rates for tamoxifen and the aromatase inhibitors are consistently low across all studies, ranging from 1% to 8%.

There are few randomized studies that have compared upfront neoadjuvant chemotherapy with neoadjuvant hormonal therapy. In a randomized trial reported by Gazet and colleagues, patients with locally advanced breast cancer received either neoadjuvant chemotherapy or hormonal therapy. The hormonal therapy consisted of a luteinizing hormone–releasing hormone (LHRH) analogue, goserelin, for premenopausal women and 4-hydroxyandrostenedione for postmenopausal women. In the chemotherapy arm, 27% of patients had a complete response and 27% had a

partial response. In contrast, no patients in the hormonal therapy arm had a complete response and only 10% had a partial response.[63] Semiglazov and associates randomized postmenopausal patients with ER-positive and/or PR-positive tumors to receive either neoadjuvant anastrozole or exemestane for 3 months or doxorubicin with paclitaxel (four 3-week cycles). Clinical objective response rates were 64% in both the hormonal therapy and chemotherapy arms. Pathologic response rates were 3% and 7% ($P > 0.05$) in the neoadjuvant hormonal therapy and chemotherapy treatment arms, respectively.[64]

ASSESSMENT OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY

One advantage of neoadjuvant chemotherapy has been the ability to monitor response to chemotherapy so that regimens can be changed in patients who are not responding and help them avoid needless toxicity. Accurate assessment of tumor response is therefore a critical component of neoadjuvant therapy. Because clinical assessment of response to chemotherapy is sometimes inaccurate and subject to substantial interobserver variability, the role of imaging modalities such as mammography, ultrasonography, and breast MRI has been explored.[65-68] Herrada and coworkers [67]found that the combination of physical examination and mammography increased the accuracy of the measurement of tumor dimensions. Other authors have found that for the measurement of the primary tumor, ultrasonography is more accurate than either clinical examination or mammography alone.[66] Kuerer and colleagues [69]studied

the role of physical examination and ultrasonography in assessing axillary lymph node status in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy. The authors found that axillary sonography was more sensitive than physical examination in detecting axillary metastases (62% vs. 45%, P ¼ 0.012). Small studies have reported an additional benefit of breast MRI for assessing response to neoadjuvant chemotherapy.[70-73]

Yeh and associates evaluated 41 women with stage II and III breast cancer who received neoadjuvant chemotherapy. All underwent physical examination, ultrasound, mammography, and breast MRI before and after each cycle of treatment, and the agreement rates of clinical response were 32%, 48%, and 55%, respectively, for mammography, ultrasound, and breast MRI compared with clinical examination. The agreement rates of pathologic response were 19%, 26%, 35%, and 71% for clinical examination, mammogram, ultrasound, and MRI, respectively, compared with the gold standard, pathologic evaluation.[71] A limitation for the routine use of breast MRI for evaluating response to neoadjuvant chemotherapy is its high cost. There is also evidence that the accuracy of breast MRI for predicting cPR depends on the type of neoadjuvant chemotherapy regimen. Higher false-negative rates have been observed in HER2/ neu-negative patients, especially in those receiving antiangiogenic agents.[74] Other imaging modalities, such as PET, nuclear medicine sestamibi uptake scans, and dynamic contrast-enhanced MRI are being evaluated for a role in assessing response to neoadjuvant therapy.

PREDICTORS OF RESPONSE TO NEOADJUVANT THERAPY

Multiple studies have evaluated factors that may be predictive of a response to neoadjuvant chemotherapy or hormonal therapy. Smaller tumor size, poorly differentiated and hormone receptor-negative tumors are significantly more likely to respond to neoadjuvant chemotherapy than larger, well-differentiated, and hormone receptor–positive tumors.[75,76] Triple-negative tumor status (ER-, PR-, and HER2/neu-negative status) is also a strong predictor for response to neoadjuvant therapy.[77]In an M.D. Anderson Cancer Center report of 1118 patients receiving neoadjuvant chemotherapy that included locally advanced and inflammatory breast cancers, patients with triple-negative disease had significantly higher rates of pCR (22%) than patients without triple-negative disease (11%; P ¼ 0.034).[78] In patients receiving neoadjuvant hormonal therapy, the degree of ER expression, HER2/neu status and Ki67 proliferation index scores have shown correlation with clinical response.[60,61] Studies are underway to identify tumor gene-expression profiles that predict for response to neoadjuvant chemotherapy or hormonal therapy. In a study of 89 patients with locally advanced breast cancer treated with neoadjuvant paclitaxel and doxorubicin, 24 genes that related to ER expression, proliferation, and immune regulation obtained using tumor DNA microarrays were associated with pCR.[79] Chang and coworkers evaluated 24 patients with locally advanced invasive breast cancer treated with neoadjuvant docetaxel chemotherapy and showed that differential expression of 92 genes correlated with response to treatment (P ¼ 0.001).[80] It is

anticipated that this type of molecular profiling will become essential for customizing therapies for patients with locally advanced breast cancer.

HANDLING OF SURGICAL RESECTION SPECIMENS AFTER NEOADJUVANT CHEMOTHERAPY

Before the examination and sampling of the surgical resection specimen it is absolutely essential to obtain as many clinical data as possible, including the radiologic report. Under ideal conditions mammography X-Rays should be sent to the pathologist together with the surgical specimen, or the pathologist should have access to the mammograms through the hospital interdepartmental information technology system.

The essential data include:

- The histologic diagnosis on the pre-treatment core biopsy.
- Axillary lymph node status.
- The length of chemotherapy and the drugs that were used.
- The size and location of the tumor prior and after chemotherapy.
- Clinical and radiologic impression of the treatment response

MASTECTOMY SPECIMEN

The mastectomy specimen should be received fresh with a mark indicating the axillary tail. Detailed clinical information including the pretreatment tumor size and location and post-treatment radiologic imaging finding are absolutely essential before examining the specimen. If lesions are thought to be multiple it is imperative to have the mammogram or at least a detailed radiology report describing the mammography data. The posterior surface (deep margin) of the mastectomy specimen is inked. The specimen is serially sectioned at a 5 mm interval from the posterior surface leaving the skin intact.

The cut surface is examined for evidence of tumor (tumor bed), residual tumor and previous biopsy site, especially at the locations corresponding to the radiology report. Grossly, the tumor bed appears as a poorly defined fibrotic area or simply fibrotic streaks; the residual tumor appears as fleshy nodules or areas. The tumor bed size and distance to margins should be measured. If a patient has had an excellent response to neoadjuvant chemotherapy, a gross lesion may not be detected, and the specimen may be sent to radiology for X-Ray to identify the previous biopsy clip (if was placed previously). The sampling method and number of blocks taken vary among institutions and are dependent on the size of the specimen and the size of the lesion. In general, the previous tumor bed should be sampled extensively; additional or entire sampling may be necessary if the initial sections don't show microscopic residual tumor.

AXILLARY LYMPH NODES

The axillary lymph node sample may include sentinel lymph node or axillary lymph node dissection after neoadjuvant chemotherapy. The specimen is handled the same way as for lymph node in the non-neoadjuvant setting. Axillary lymph nodes are usually smaller and atrophic therefore more difficult to identify after neoadjuvant chemotherapy.

CHEMOTHERAPY INDUCED CHANGES IN BREAST CANCER

The neoadjuvant chemotherapy effect is recognized as a fibrous or fibromyxoid area containing patchy lymphocytes, histiocytes, and absence of normal breast ducts and TDLUs. Hemosiderin laden macrophages and foreign body giant cells are also present in the tumor bed representing previous biopsy site. When the tumor bed is extensively sampled and no tumor cells are identified, this is termed complete pathologic response. If residual cancer cells are present, they may be seen as infiltrating cords and nests , or sparse and singly dispersed cells mimicking histiocytes. On the other hand, collections of histiocytes may resemble residual tumor cells. Immunohistochemical stains with cytokeratin and CD68 will help in differentiating tumor cells from histiocytes . Residual tumor nests may show marked retraction artifact in the fibrous stroma mimicking lymphovascular invasion; immunohistochemical stain for lymphatic channel marker D2-40 may be useful to distinguish tissue retraction from lymphatic invasion. Specimens containing residual tumor cells are labeled as showing signs of a partial pathologic response. Residual

cancer cells surviving chemotherapy may show a spectrum of changes, which are evident in the invasive as well as the in-situ component of the tumor. Most common chemotherapy effects include nuclear hyperchromasia, nuclear pleomorphism and cytoplasmic changes such as hypereosinophilic cytoplasm and vacuolization . The size or extent of the residual breast cancer is measured as the largest contiguous focus of residual carcinoma or the number of tumor foci encompassing the area of tumor bed. The margins of residual tumor (DCIS and invasive carcinoma) should be evaluated and distance reported.

CHANGES IN LYMPH NODES

Axillary lymph nodes may become small and atrophic after neoadjuvant chemotherapy. Microscopically, lymph nodes may show depletion of lymphocytes, fibrosis and collections of histiocytes. The latter two features are indications of prior metastases that have responded completely to chemotherapy. Efforts should be made to identify residual tumor cells in these lymph nodes and report the presence or absence of treatment effects

ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY

Miller-Payne System	Histopathologic findings
Grade 1	No change or some alteration to individual malignant cells, but no reduction in overall cellularity
Grade 2	A minor loss of tumor cells, but overall cellularity still high; up to 30% loss
Grade 3	Between an estimated 30% and 90% reduction in tumor cells
Grade 4	A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; >90% loss of tumor cells
Grade 5	No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastotic stroma remains, often containing macrophages; however, ductal carcinoma in situ may be present.

Honkoop Classification

pCR	No cancer in breast or axillary nodes
Minimal Residual Disease	Only microscopic RD in breast or axillary nodes
Macroscopic Residual Disease	Macroscopic RD in breast or axillary nodes

Chevallier Classification

Grade 1	No cancer in breast or axillary nodes
Grade 2	Only *in situ* carcinoma remains, nodes are negative
Grade 3	Invasive carcinoma with stromal fibrosis
Grade 4	No or few modifications of stromal fibrosis

Sataloff Classification

Primary Tumor		Axillary Nodes		
T-A	Total or near-total therapeutic effect	N-A	N-	Evidence of therapeutic effect
T-B	> 50% therapeutic effect	N-B	N-	No evidence of therapeutic effect
T-C	< 50% therapeutic effect	N-C	N+	Evidence of therapeutic effect
T-D	No therapeutic effect	N-D	N+	No evidence of therapeutic effect

MATERIALS AND METHODS

STUDY CENTRE: Institute of General Surgery , Madras Medical College and Rajiv Gandhi Government General Hospital , Chennai

DURATION OF STUDY: May 2017- September 2018

STUDY DESIGN: Observational study

SAMPLE SIZE: 30

INCLUSION CRITERIA:

- Age > 18 years
- Locally advanced carcinoma
- Willing for follow up

EXCLUSION CRITERIA

- Prior Breast Surgery
- Prior radiotherapy to breast
- Metastatic disease

ETHICS CLEARANCE: Yes

METHODOLOGY

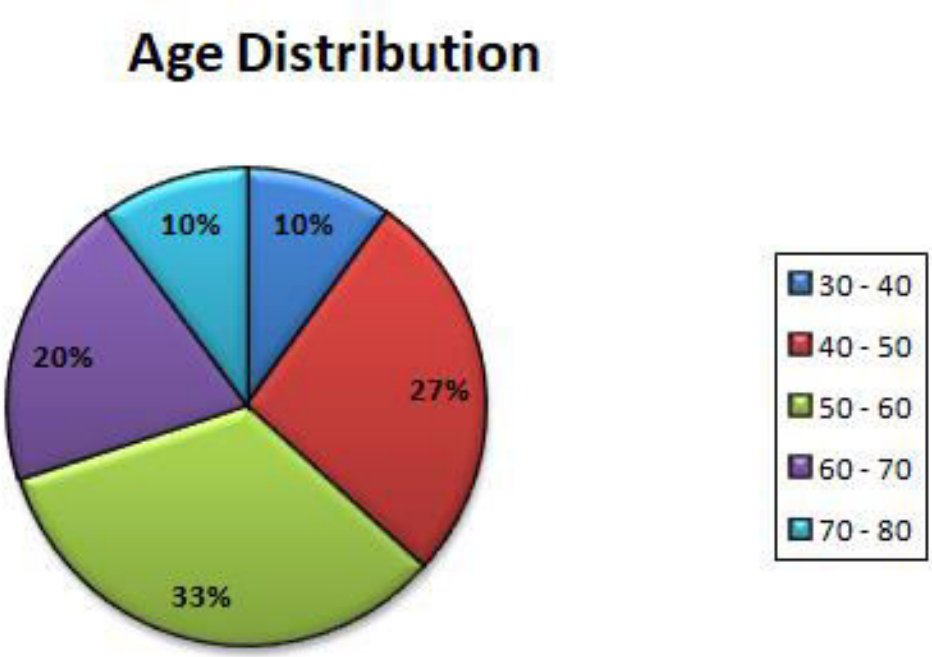
- Patients aged >18 years presenting with malignant breast lump were evaluated.
- Diagnosis confirmed by core needle biopsy and grade and hormonal status assessed and metastatic work up done.

- Thirty patients who fulfilled the inclusion criteria were chosen and were sent for neoadjuvant chemotherapy.(FAC OR FAC+PACLITAXEL REGIMEN)

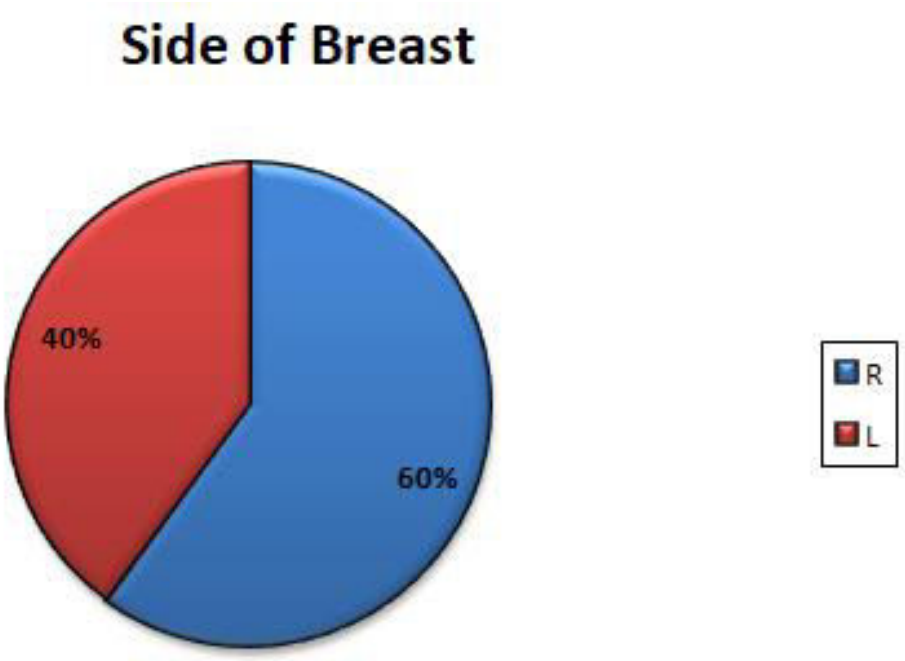
- Patients were followed up and response of tumor assessed clinically and modified radical mastectomy was done.

- Specimen was analyzed for pathological response and observations made.

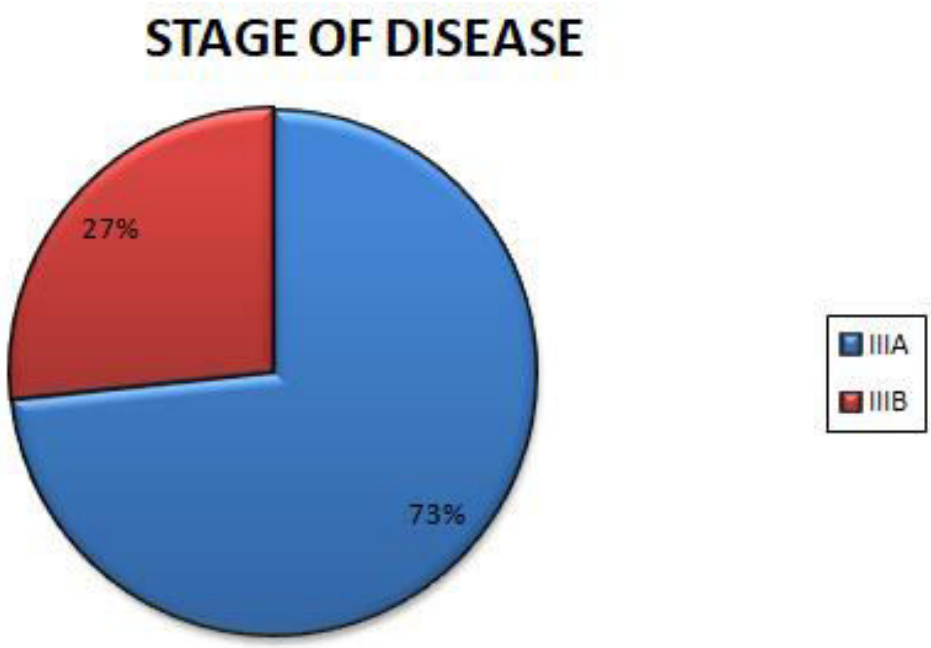
RESULTS



Majority of the population belonged to the age group of 50-60 (33%)



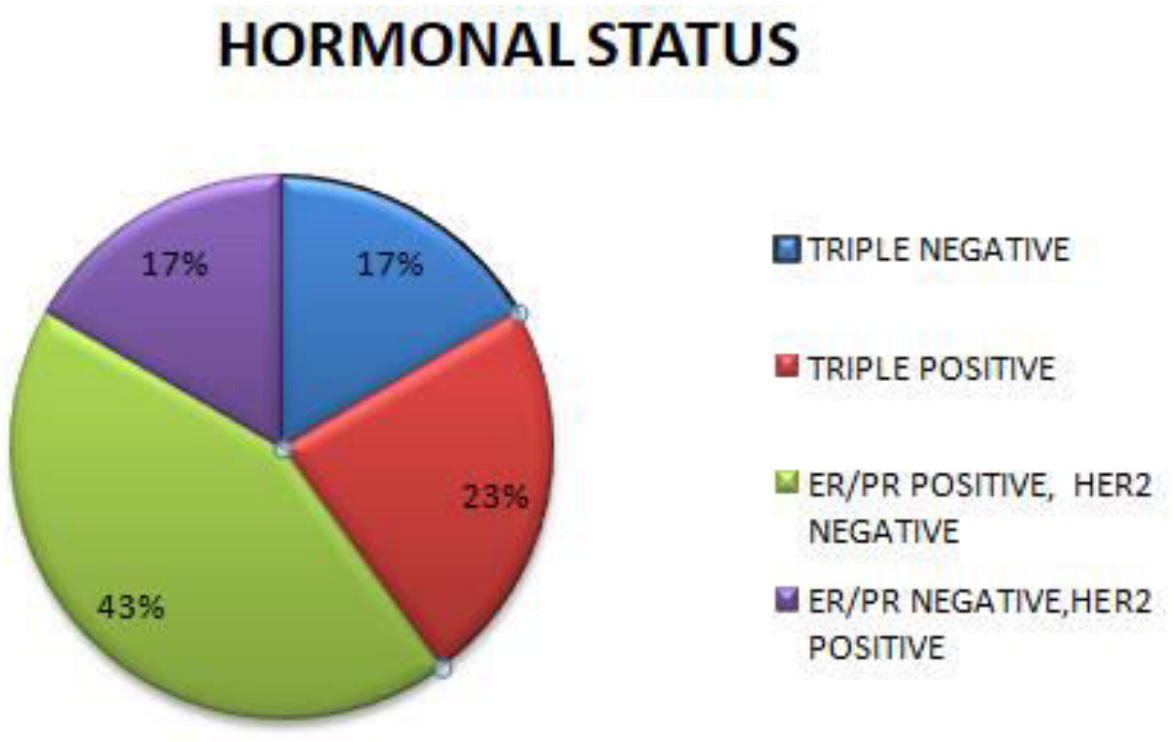
60% of the patients had right sided breast carcinoma



Of the 30 patients having locally advanced carcinoma breast

- 73% belonged to stage IIIA

- 27% belonged to stage IIIB

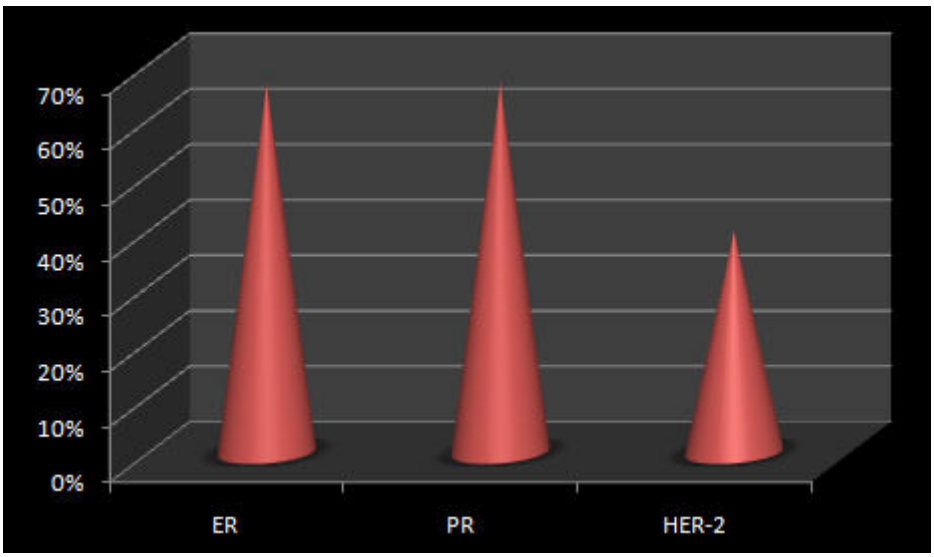


- Almost half of the patients were ER positive, PR positive and HER2 negative.

- 23% of the patients were triple positive.

- Triple negative and her 2 positive patients were of equal distribution (17%).

PREVALENCE OF HORMONAL RECEPTOR STATUS

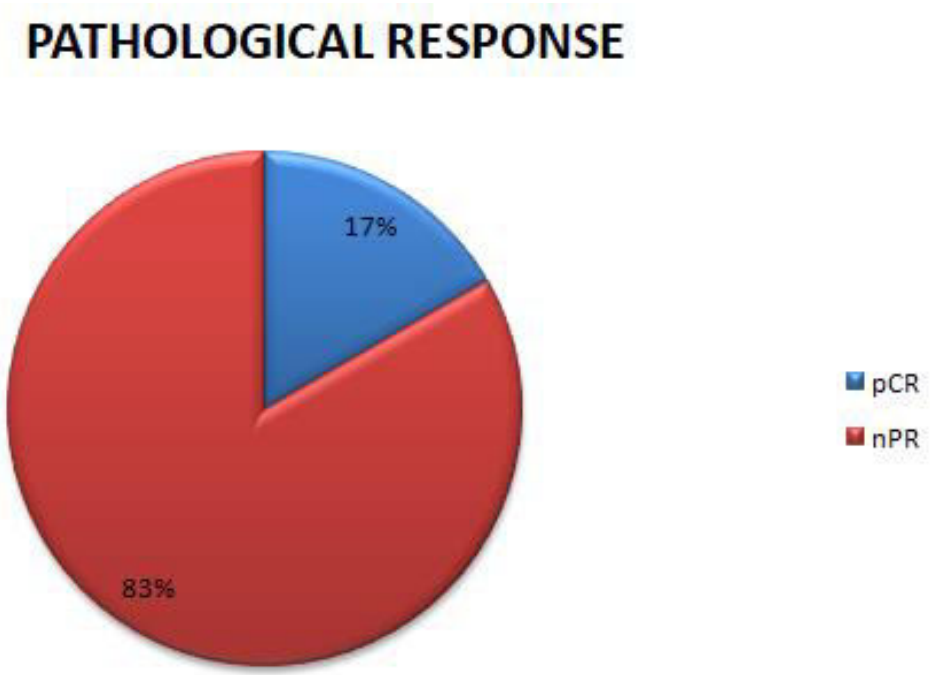


Percentage of ER and PR positive tumors were 67% each.

Percentage of HER2 positive tumors were 40%.

Postoperative assessment of specimen was done and pathological response graded according to Chevalier classification.

- 53% were of grade 4
- 30% were of grade 3
- 13%were of grade 2
- 3% was of grade 1



- Only 17% of patient population showed pathological response to NACT

- 83% were non responders

DISCUSSION

In India, majority of patients present at locally advanced or at metastatic stages at the time of diagnosis. According to various studies, majority of carcinoma breast cases in the west report in stages I and II of disease, whereas in India 45.7% report in advanced stages. This study was aimed to study the response of locally advanced carcinoma breast to neoadjuvant chemotherapy.

Majority of the study population were of the age group of 50-60. Studies suggest that the disease peaks at 40–50 years in Indian women.[81] Trends for 5-year age distribution among different registries showed a peak relative proportion between 45 and 49 years in all registries except in north eastern registries.[82]

60% of the study population had right sided breast carcinoma.This is against the studies reporting higher incidence of left sided invasive and in situ lesions by Faidah Badru et al though their results weren't statistically significant.[83]

73% of the study population belonged to stage IIIA and 27% belonged to stage IIIB.Assessment of hormonal status revealed 43% with ER and PR positive and HER2 negative and 21% of triple positive and 17% of triple negative and ER/PR negative but HER2 positive each. Presence of ER and PR in invasive carcinoma correlates

positively with survival and is an important prognostic factor. The determination of ER, PR and HER-2 in breast cancer has become part of the standard workup.ER and PR positive tumors were 67% each and HER 2 was 40%.

Different study group from India	ER %	PR %	HER-2 positivity by IHC %	p53 %
Desai *et al.*[19]	32.6	46.1		—
Dutta *et al.*[21]	24	30	46.3	—
Ambroise *et al.*[3]	59	51	27.10	—
Vaidyanathan *et al.*[13]	50.2	46.9	43.2	—
James *et al.*[22]	—	—	29.0	—
Munjal *et al.*[12]	41.1	41.1	40.2	—
This study	47.6	48.8	29.6	69.2

ER – Estrogen receptor; PR – Progesterone receptor; IHC – Immunohistochemistry; HER-2 – Human epidermal growth factor-2

Image reference –Rashmi Patnayak et al [84]

The prevalence of ER and PR positive status was higher in our study when compared with previous studies and HER 2 positivity was almost same as the previous studies.

Post MRM specimen assessment and classification of pathological response according to Chevalier classification revealed 3% of grade 1, 13% of grade 2, 30% of grade 3 and 53% of grade 4 responses each. Overall 17% of study population showed complete pathological response and 83% were non responders. This is in line with

12% response in a Cochrane study [85]. Other investigators have shown that a pCR in the primary tumor occurs in 3% to 16% of patients with operable breast cancer and LABC.[85]

In an early study, Lippman[86] et al reported on the relationship between estrogen receptor status and response rate to cytotoxic chemotherapy in the metastatic breast cancer setting. They found statistically increased objective response rates to chemotherapy in patients with low or absent ER values, compared with patients with higher ER values. In the neoadjuvant setting, the finding that ER negative tumors were more likely associated with higher response rates than ER-positive tumors has been reported by both Bonadonna et al and Mauriac et al[85].The higher prevalence of ER positivity could account for the lower response rate to neoadjuvant chemotherapy in our study.

CONCLUSION

Locally advanced breast cancer (LABC) occurs relatively infrequently and poses a significant clinical challenge. Even with combined-modality therapy and the use of novel drugs, long-term disease-free survival is approximately 50%-70%[88], indicating that the optimal therapeutic approach for these patients has not yet been reached. Neo-adjuvant systemic therapy integrated into a multimodality program is the established treatment in LABC. The choice of the optimal chemotherapy regimen and the duration of treatment have been extensively assessed in induction systemic chemotherapy but no consensus has been developed so far. One more issue that was subject of extensive debate in NCT is the importance of response to initial chemotherapy. This variable is an established key criterion of the early era of induction chemotherapy trials. It represents the main advantage of preoperative therapy, which is the feasibility to monitor tumor response and to tailor subsequent treatment based on response. Nevertheless, no strong correlation of clinical and pathologic responses has been demonstrated. It has been established that a pCR in the primary tumor is associated with improved disease-free survival and patients without axillary lymph node metastases after neoadjuvant chemotherapy have improved disease-free survival. Identifying which tumors are most likely to respond to specific agents and regimens could significantly improve prognosis. Clinical management of LABC could be modified based on advances in our knowledge of cancer biology and genomic profiling to a highly effective individualized approach.

Identifying which tumors are most likely to respond to specific agents and regimens could significantly improve prognosis. Clinical management of LABC could be modified based on advances in our knowledge of cancer biology and genomic profiling to a highly effective individualized approach.

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PROFORMA

Name: Age:

Menstrual Status

1. Pre chemo status

- Lump size
- Axillary status
- Mammogram report –
- Core needle biopsy report-
- Staging workup
- Tumor stage

2. Chemotherapy details

3. Post chemo status

- Lump size -
- Axillary status –
- Mammogram report(if any)
- Tumor stage
- Post op biopsy report :

INFORMATION SHEET

- **TITLE**: "ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED CARCINOMA BREAST"

Name of Investigator: Dr.Aarthi V.S..

Name of Participant:

Purpose of Research: To assess the pathological response to neoadjuvant chemotherapy in carcinoma breast

Study Design: Prospective Observational Study

Study Procedures: Patient will be subjected to routine investigations, mammogram,core needle biopsy and staging workup.patient will be sent for neoadjuvant chemotherapy and response will be assessed after mastectomy pathologically.

Possible Risks: No risks to the patient

Possible benefits

To patient : A better understanding of their problem so has to devise a plan of management which suits their needs.

To doctor & to other people: If this study gives positive results, it can help determine the role of pathological response in the treatment of patients with LABC. This will help in providing better and complete treatment to other patients in future.

Confidentiality of the information obtained from you: The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared

Can you decide to stop participating in the study: Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time

How will your decision to not participate in the study affect you: Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail : **"ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST"**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

In Patient Number :

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the Ethics committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment ❑

Signature/thumb impression

Patient's Name and Address

CERTIFICATE – II

This is to certify that this dissertation work titled "**ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST"** of the candidate **Dr. Aarthi V.S.** with registration Number **22161101** for the award of **M.S degree** in the BRANCH -1 of **General Surgery**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **7%** percentage of plagiarism in the dissertation.

Guide and Supervisor sign with seal

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.Aarthi.V.S.
I Year Post Graduate in M.S. General Surgery
Institute of General Surgery
Madras Medical College
Chennai 600 003

Dear Dr.Aarthi.V.S,

The Institutional Ethics Committee has considered your request and approved your study titled **"ASSESSMENT OF CLINICAL AND PATHOLOGICAL RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY IN BREAST CARCINOMA " - NO.16062017**

The following members of Ethics Committee were present in the meeting hold on **06.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5.Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6.Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7.Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

21/6/17

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

Analysed Document: thesis.docx (D42536132)
Submitted: 10/14/2018 7:59:00 PM
Submitted By: aashruthivs@gmail.com
Significance: 7 %

Sources included in the report:

http://www.health.govt.nz/publication/management-early-breast-cancer-evidence-based-best-practice-guideline
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Instances where selected sources appear:

29

MASTERCHART

S.NO	NAME	AGE	SIDE	TUMOUR	NODE	STAGE	CORE NEEDELE REP	HORMONAL STATUS			CHEMOTHERAPY	CHEVALIER CLASS	PATHOLOGICAL RESPON
								ER	PR	HER 2			
1	saroja	55	R	T3	N1	IIIA	INVASIVE NOS	N	N	P	FAC	3	NO
2	kuttiyamr	60	R	T4a	N1	IIIB	INVASIVE NOS	P	P	P	FAC	4	NO
3	jaya	45	R	T2	N2	IIIA	INVASIVE NOS	P	P	P	FAC+PACLITAXEL	4	NO
4	vijaya	47	R	T3	N1	IIIA	INVASIVE NOS	P	P	N	FAC	3	NO
5	visalaksh	38	R	T4a	N1	IIIB	INVASIVE NOS	P	P	N	FAC	3	NO
6	rani	68	L	T4b	N1	IIIB	INVASIVE NOS	N	N	N	FAC+PACLITAXEL	3	NO
7	uma	72	R	T3	N2	IIIA	INVASIVE MEDULLA	P	P	P	FAC	2	YES
8	jothi	66	L	T3	N2	IIIA	INVASIVE NOS	P	P	N	FAC+DOCETAXEL	3	NO
9	prabha	44	R	T3	N1	IIIA	INVASIVE NOS	P	P	N	FAC	4	NO
10	shahida l	42	L	T4a	N1	IIIB	INVASIVE NOS	P	P	P	FAC+PACLITAXEL	4	NO
11	kala	39	L	T3	N2	IIIA	INVASIVE NOS	N	N	N	FAC	3	NO
12	santha	55	R	T4a	N1	IIIB	INVASIVE NOS	P	P	N	FAC	3	NO
13	thaiyalna	50	R	T3	N1	IIIA	INVASIVE NOS	P	P	N	FAC	2	YES
14	geetha	64	L	T3	N1	IIIA	INVASIVE NOS	P	P	N	FAC+PACLITAXEL	4	NO
15	mary	57	L	T4a	N1	IIIB	INVASIVE NOS	P	P	P	FAC	3	NO
16	annapoc	58	R	T3	N1	IIIA	INVASIVE NOS	N	N	P	FAC	3	NO
17	vidhya	68	R	T3	N2	IIIA	INVASIVE NOS	N	N	P	FAC	3	NO
18	saroja	70	R	T3	N2	IIIA	INVASIVE NOS	P	P	N	FAC+PACLITAXEL	2	YES
19	shanthi	55	R	T3	N1	IIIA	INVASIVE NOS	N	N	P	FAC	4	NO
20	parimala	52	R	T3	N1	IIIA	INVASIVE NOS	N	N	N	FAC	3	NO
21	jagadhar	48	R	T2	N2	IIIA	INVASIVE NOS	P	P	N	FAC	3	NO
22	thulasi	44	R	T3	N1	IIIA	INVASIVE NOS	P	P	P	FAC	2	YES
23	jeyamma	37	L	T3	N1	IIIA	INVASIVE NOS	N	N	P	FAC	3	NO
24	jayalaksh	49	L	T2	N2	IIIA	INVASIVE NOS	P	P	N	FAC	3	NO
25	muneesh	52	R	T2	N2	IIIA	INVASIVE NOS	P	P	N	FAC	4	NO
26	govindha	43	L	T4a	N0	IIIB	INVASIVE NOS	N	N	P	FAC+PACLITAXEL	4	NO
27	rose	61	L	T4b	N1	IIIB	INVASIVE NOS	P	P	N	FAC	4	NO
28	malathi	70	L	T3	N1	IIIA	INVASIVE NOS	N	N	N	FAC	3	NO
29	shenbag	55	L	T2	N2	IIIA	INVASIVE NOS	P	P	P	FAC	4	NO
30	sumathy	52	R	T3	N1	IIIA	INVASIVE NOS	P	P	N	FAC+PACLITAXEL	3	NO